REMARKS

Applicants respectfully request reconsideration of the present application in view of the following comments.

I. Status of the Claims

No claim amendment is made in this response. Claims 1-95 are pending with claims 32-35, 39, 41-43 and 45-95 withdrawn from consideration. Upon allowance of the product claims, Applicants respectfully request rejoinder of the corresponding method claims.

II. Rejection of Claims under 35 U.S.C. §103(a)

A. Reiner and Ryde

Claims 1-15 and 27-31 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,711,961 to Reiner et al. ("Reiner") in view of U.S. Patent No. 6,375,986 to Ryde et al. ("Ryde"). Applicants respectfully traverse the rejection.

With a correct read of the references, the combined teachings of the cited art fail to render the claimed invention obvious.

(1) The Examiner incorrectly interprets the claim limitation "effective average particle size"

The Examiner incorrectly equates a teaching in Reiner with the following claim element: effective average particle size of less than 2000 nm.

First, Reiner fails to teach the claimed particle size. Reiner merely states in passing that drug particles can occur in the micron range. According to the Examiner, the teaching of Reiner that the drug particles are "in the micron size range" is equivalent to the particle size distribution element required by the claimed invention. This is technically incorrect. Reiner merely mentions its drug particle size in passing, at column 4, lines 64-65: "A syrup, possibly suitably

flavored, containing the micronized drug in suspension. . . ." This bare teaching is insufficient to enable one of ordinary skill in the art about an effective average particle size as defined in the instant claims.

For example, by definition, "micron size range" typically encompasses the particle size between 1 micron and 999 microns. In contrast, the instant claim requires an ***effective average particle size*** of less than 2000 nm. As explicitly defined in the specification, "an effective average particle size of less than 2000 nm" means that at least 50% of the nimesulide particles have a particle size less than 2000 nm. *See* page 19, paragraph [0066]. As such, "an effective average particle size of less than about 2000 nm" is represented by a bell-shaped curve with a peak of particle size around 2000 nm. Accordingly, the brief mentioning of drug particle size in the micron size range of between 1 and 999 microns (i.e., Reiner) fails to teach or suggest the particle size distribution of the claimed invention. Therefore, Reiner fails to teach this limitation of the claims.

The following question logically follows: If Reiner does not meet the claimed limitation and Ryde does, why would one skilled in the art modify the micron-sized drug particles in Reiner so that they have a size distribution where 50 % of the particles are smaller than 2000 nm and 50% are larger than 2000 nm as taught by Ryde? The rejection fails to provide a valid answer to this question for at least the following reasons.

(2) The reason to combine Reiner and Ryde is lacking.

The Examiner asserts that "the only aspect of the claimed invention not disclosed by Reiner et al." is "stabilizing agents adsorbed onto the surface of the micron-sized nimesulide particles" (final Office Action, page 7, lines 14-18). The Examiner contends that Ryde compensates for the acknowledged deficiencies of Reiner.

(i) A lack of evidence that the combination of reference cannot be made does not support the conclusion that the combination of references is obvious.

The Examiner's rationale for combining the references is that one skilled in the art would not expect the advantage of Ryde to diminish the advantage of Reiner. Such a rationale is not based on fact. A lack of evidence teaching away from combining the references as suggested by the Examiner is not evidence of the obviousness of the invention in view of the references. This new test created by the Examiner is clearly not based upon any patent law premise. Indeed, this is an indication that the rejection rationale is based on nothing but impermissible hindsight as articulated below.

(ii) Reiner and Ryde are directed to unrelated technologies.

Both of the cited references are directed to solving vastly different problems identified in the relevant prior art, and there is no suggestion or teaching in either reference that the disclosed technology could be applicable to the claimed invention. Because Reiner and Ryde are directed to unrelated technologies and advantages, it is only with the aide of impermissible hindsight gleaned from the instant claims that the Examiner was able to combine these references.

For example, Reiner addresses the problem present in the prior art regarding unpalatability of a dosage form by utilizing a lacquer-coated chewing gum tablet, which achieves a balance of plasmatic and haematic absorption of the drug present in the dosage form. See column 5, lines 54-60. Reiner does not expressly or impliedly teach that the described micronized drug particles are unstable in any way, which could have prompted a solution by requiring a surface stabilizer adsorbed on the surface of the micronized drug particles. Nor does Reiner suggest that the micron sized drug particles do not dissolve adequately, thus requiring the need for further size reduction to increase the dissolution of the drug particles.

It is well known that ultra fine particles are unstable due to their surface charge and properties, etc. and they tend to agglomerate and aggregate to form larger particles to regain stability. Utilizing steric surface stabilizers is one way to solve the stability problem because surface stabilizers can adsorb on the surface of the nanoparticulate drug particles, thereby preventing agglomeration or aggregation. Ryde, on the other hand, addresses the problem present in the prior art regarding redispersibility of solid dose particulate compositions by discovering a synergistic combination of a polymeric surface stabilizer and dioctyl sodium sulfosuccinate (DOSS), which results in a superior redispersibility profile of the solid dose composition. See abstract, and column 5, lines 60-66.

One skilled in the art would not have any reason to combine these references because the lacquer coating (Reiner) and the synergistic combination of surface stabilizers (Ryde), or the unpalatability (Reiner) and redispersibility (Ryde), have no correlation to each other. Thus, only with the use of impermissible hindsight is the Examiner able to select these two vastly different prior art references and selects specific excerpts from them to construct the claimed invention. A rationale to combine references cannot be based upon hindsight alone and there is no other articulated reason espoused by the Examiner explaining why one skilled in the art would combine the teachings of Reiner and Ryde. Accordingly, the rejection is in error.

(iii) The Examiner misinterprets Applicants' characterization of the claimed invention

In an attempt to bridge the gap between the prior art and the claimed invention (i.e., to justify a rejection that lacks a reason to combine the cited references), the Examiner erroneously states that "the claimed composition as depicted in (A) is simply a "zoomed-in" view of the micronized drug layer of (B) as disclosed by Reiner et al., minus the surface stabilizer adsorbed onto the surface of the micronized drug particles" (final Office Action, page 7, lines 1-3).

This interpretation of the claimed invention errs in at least two aspects: (a) the Examiner takes the drug layer of Reiner's composition out of context and puts it in a "vacuum" to fit in the

claim elements; and (b) the Examiner attempts to fill in the information missing from the prior art based on the knowledge or the claimed invention, again, with the aid of impermissible hindsight.

Concerning point (a), the MPEP urges that the Examiner should consider the prior art as a whole rather than isolating an element from prior art and comparing it with the claimed invention. MPEP 2141.02 ("Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole.")

Turning to point (b), the Examiner would not have had "zoomed in" the drug layer of Reiner's composition in the absence of any knowledge from the claimed invention. This is because, as discussed below, one skilled in the art would not have any reason to modify Reiner's composition in view of Ryde's teaching.

Accordingly, the Examiner has failed to meet the initial burden to establish a *prima facie* case of obviousness.

(3) The modification of Reiner in view of Ryde would destroy the intended purpose of a component in Reiner

For arguments' sake, Applicants assert that even if the Examiner presented a valid reason based in fact to modify Reiner in view of Ryde, such a modified Reiner would destroy the intended purpose of certain components of Reiner.

In order to teach the claimed limitation of a surface stabilizer on the drug particles, the Examiner appears to suggest that one skilled in the art when combining the teachings of Reiner and Ryde would remove the lacquer layer of Reiner's composition, which contains celluloses and polyethylene glycols, and make these celluloses and polyethylene glycols the surface stabilizers which would then be adsorbed on the surface of the drug particles. This logic is contrary to MPEP 2143.01, "[i]f [a] proposed modification would render the prior art invention being

modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)" In the present case, the change of the lacquer coating into surface stabilizers would require removal of the lacquer coating to obtain the claimed invention, which is a deviation from the intended purpose of Reiner's composition.

Alternatively, if the Examiner suggests adding a surface stabilizer to Reiner's composition in view of Ryde's teaching, this modification would result in a lacquer-coated gum tablet having surface stabilizers adsorbed to the surface of drug particles which are in the micron-size range. There is no teaching in either of the cited references that micron-sized drug particles need surface stabilizers to prevent aggregation. There is simply no basis in the cited references for the Examiner to reach this conclusion.

B. Reiner, Ryde and Tertiary References

Claims 1, 10-13 and 15-26 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over Reiner and Ryde in view of U.S. Patent No. 5,552,160 to Liversidge *et al.* ("Liversidge"). Claims 1 and 16-26 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over Reiner and Ryde in view of Singh *et al., Analytical Profiles of Drug Substances and Excipients,* 28: 197-249 (2001) ("Singh") and U.S. Patent No. 5,510,118 to Bosch et al. ("Bosch"). Claims 1, 36-38 and 40 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over Reiner and Ryde in view of Singh and the Merck Index, 12th ed., Merck & Co., Codeine, pp. 416-417 (1996). Finally, claims 1 and 44 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over Reiner and Ryde in view of U.S. Patent No. 5,776,563 to Buhl et al. ("Buhl"). Applicants respectfully traverse all of these rejections.

The teachings of Reiner and Ryde are discussed *supra*. Liversidge, Singh, and Bosch are cited for the alleged teaching of T_{max}, C_{max} or AUC profile of nimesulide. The Merck Index is cited for the alleged teaching that codeine has analgesic properties. Finally, Buhl is cited for the

alleged teaching of sterile filtration. Because none of the tertiary references remedy the deficiencies of Reiner and Ryde as discussed above, withdrawal of the rejections is respectfully requested.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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